Malignancies in Inflammatory Bowel Disease

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Abstract: BACKGROUND Inflammatory bowel disease (IBD) is a chronic inflammatory disorder, primarily of, but not restricted to, the gut. Association between IBD and cancer has been clearly established and is uniformly accepted. SUMMARY IBD patients are at particular risk for intestinal and extraintestinal cancers. There are 2 underlying mechanisms: (1) IBD-related inflammation triggers initiation and progression of tumor formation. This particularly results in the development of colorectal cancer, small bowel adenocarcinoma, intestinal lymphoma, anal cancer, and cholangiocarcinoma. (2) Immunosuppressive drugs exhibit carcinogenic properties such as shown for azathioprine and anti-TNF promoting lymphoproliferative malignancies and melanoma and non-melanoma skin cancer. However, within the last years, IBD-related cancer incidence and prevalence have been decreasing, which might be attributed to better treatment options and surveillance strategies. Moreover, novel biological drugs have been introduced in clinical practice and have dramatically changed long-term IBD management. Therefore, we sought to summarize up-to-date knowledge about (1) overall cancer risk; (2) risk and protective factors for cancer development; and (3) inflammation- and immunosuppression-related malignancies in the current anti-TNF era of IBD. Key Messages: Recent studies and meta-analyses questioned the excess rates of cancer in IBD patients. However, IBD still is associated with cancer development due to ongoing intestinal inflammation and the use of potential carcinogenic drugs. Patients should be educated about the increased risk of cancer with IBD and IBD drugs. However, they should also be informed that most malignancy subtypes are possibly preventable by controlling intestinal inflammation and by using adequate screening strategies.

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Malignancies in Inflammatory Bowel Disease

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Keywords
Inflammatory bowel disease · Malignancy · Cancer · Anti-TNF · Immunosuppression

Abstract
Background: Inflammatory bowel disease (IBD) is a chronic inflammatory disorder, primarily of, but not restricted to, the gut. Association between IBD and cancer has been clearly established and is uniformly accepted. ***Summary:*** IBD patients are at particular risk for intestinal and extraintestinal cancers. There are 2 underlying mechanisms: (1) IBD-related inflammation triggers initiation and progression of tumor formation. This particularly results in the development of colorectal cancer, small bowel adenocarcinoma, intestinal lymphoma, anal cancer, and cholangiocarcinoma. (2) Immunosuppressive drugs exhibit carcinogenic properties such as shown for azathioprine and anti-TNF promoting lymphoproliferative malignancies and melanoma and nonmelanoma skin cancer. However, within the last years, IBD-related cancer incidence and prevalence have been decreasing, which might be attributed to better treatment options and surveillance strategies. Moreover, novel biological drugs have been introduced in clinical practice and have dramatically changed long-term IBD management. Therefore, we sought to summarize up-to-date knowledge about (1) overall cancer risk; (2) risk and protective factors for cancer development; and (3) inflammation- and immunosuppression-related malignancies in the current anti-TNF era of IBD. ***Key Messages:*** Recent studies and meta-analyses questioned the excess rates of cancer in IBD patients. However, IBD still is associated with cancer development due to ongoing intestinal inflammation and the use of potential carcinogenic drugs. Patients should be educated about the increased risk of cancer with IBD and IBD drugs. However, they should also be informed that most malignancy subtypes are possibly preventable by controlling intestinal inflammation and by using adequate screening strategies.

Introduction

Inflammatory bowel disease (IBD) with its 2 subtypes, Crohn's disease (CD) and ulcerative colitis (UC), is characterized by a chronic inflammation of the intestine [1]. However, it has been known for years that inflammatory activity in IBD is not restricted to the gut, but can occur at various extraintestinal sites [2]. IBD is a common disorder in the Western Hemisphere with an estimated

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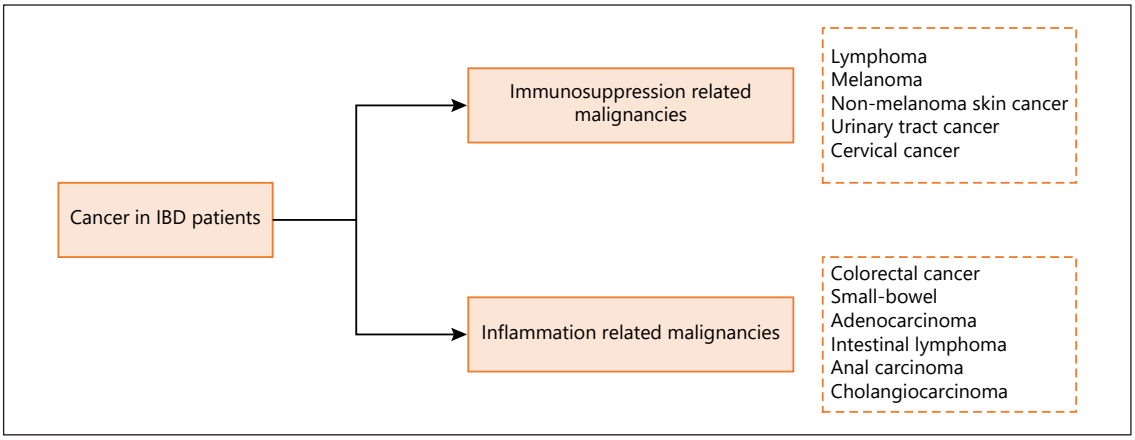

Fig. 1. Classification of cancer in IBD patients into the 2 categories of inflammation-related and immunosuppression-related malignancies. IBD, inflammatory bowel disease.

prevalence of 246.7/100,000 for CD and 286.3/100,000 for UC [3]. Cancer represents the second leading cause of death worldwide (after cardiovascular diseases); it is estimated that one out of 2 individuals will suffer from malignancy during life [4]. Given the frequency of these 2 diseases, co-occurrence does not necessarily imply association or causality. However, the concept of inflammation resulting in cancer development is clearly established. The German pathologist Rudolf Virchow first suggested a causal relation between inflammatory processes and tumor formation based on his observations of leukocytes within cancer tissue [5]. This was back in 1863 [6]. One hundred fifty years later, numerous inflammatory processes have been linked to cancer development such as viral hepatitis (to hepatocellular carcinoma), *Helicobacter pylori* gastritis (to gastric cancer), pancreatitis (to pancreatic adenocarcinoma), or mononucleosis (to lymphoma). In IBD, inflammation has been linked to colorectal cancer development; studies have shown a 2-fold increase in the risk for colorectal carcinoma, particularly in patients with extensive colonic inflammation and longer disease duration [7]. Ongoing colonic inflammatory insults result in initiation and progression of cancer formation through step-wise mechanisms [8].

Increased cancer risk in IBD goes beyond intestinal malignancies. Extraintestinal cancer appears to occur more frequently than it would be expected from the general population [7, 9, 10]. Examples here are cholangiocarcinoma, lymphoma, and melanoma and nonmelanoma skin cancer. Case-control and large nation-wide cohort studies have revealed that some of these malignancies are triggered by immunosuppressive treatment such as thiopurines or anti-TNF rather than by intestinal inflammation [11–16]. Based on these observations, IBD-related malignancies are currently classified into 2 groups: (1) cancers resulting from IBD activity (*inflammation-related*) and (2) cancers related to IBD treatment (*immunosuppression-related*; Fig. 1) [7]. Some cancer types such as EBV-related primary intestinal lymphoma in patients exposed to thiopurines are attributed to both inflammation and IBD treatment. Besides immunosuppressive drugs' carcinogenic potential, their chemopreventive properties should also be kept in mind, such as described for 5-ASA [17–19].

Within the last years, IBD-related cancer incidence and prevalence have been decreasing, which might be attributed to better treatment options and surveillance strategies [7, 9, 20]. In addition, new biological drugs have been introduced in clinical practice and have dramatically changed long-term IBD management. Therefore, we sought to summarize up-to-date knowledge about (1) overall cancer risk; (2) risk and protective factors for cancer development; and (3) inflammation- and immunosuppression-related malignancies in the current anti-TNF era of IBD. This review will not discuss the available treatment options for specific cancer subtypes.

Epidemiology

Malignancy Overall

Several studies from nation-wide cohorts revealed excess risk of cancer in IBD patients, more so in CD than UC, particularly for gastrointestinal cancer (small bowel

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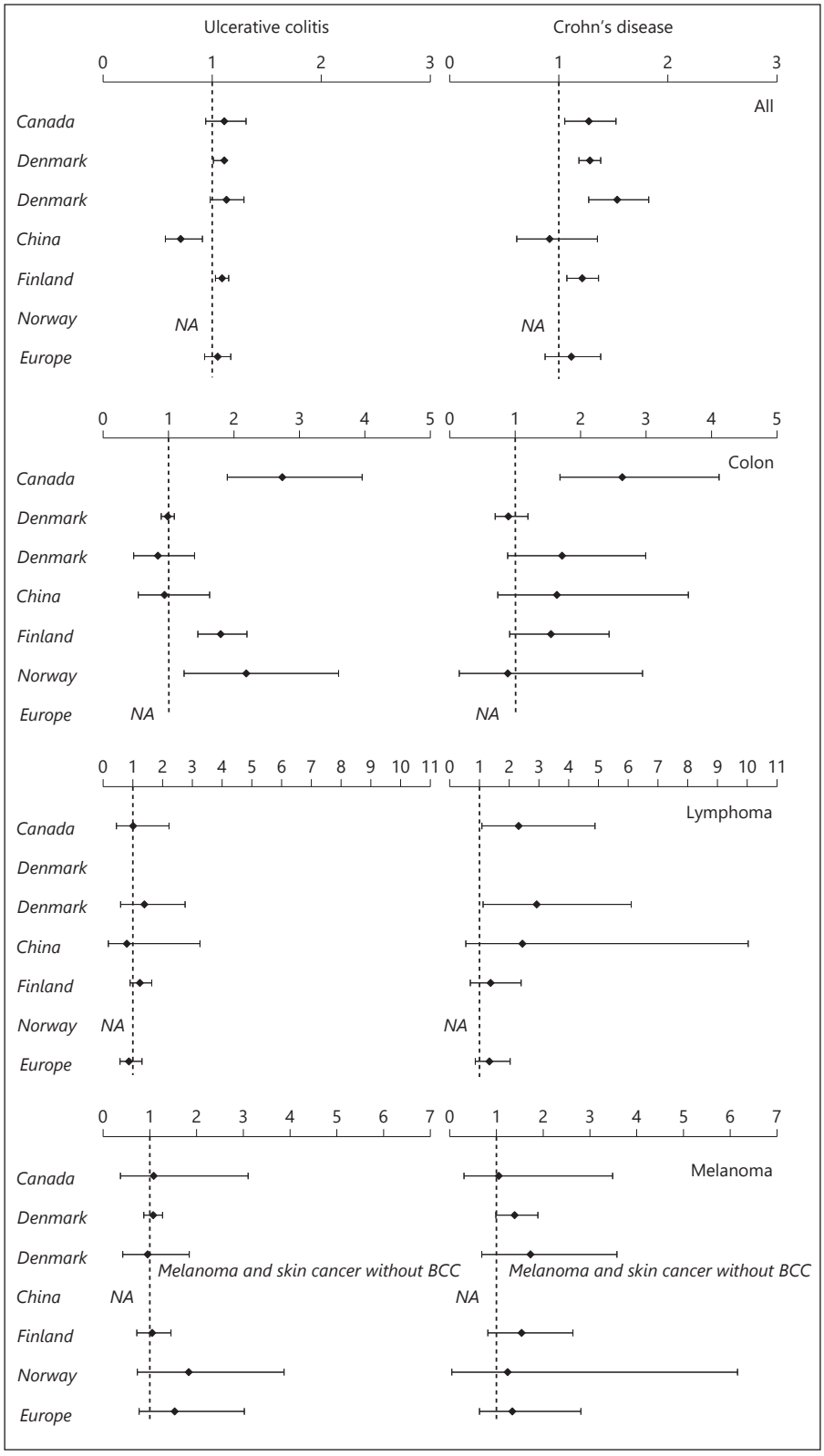

Fig. 2. Forest plots for development of cancer overall, colon cancer, lymphoma, and melanoma based on the major available cohort studies. All data are stratified by IBD subtype (CD vs. UC). The results are shown from the cohort studies of Bernstein et al. (Canada) [70], Kappelman et al. (Denmark) [10], Jess et al. (Denmark) [9], So et al. (China) [71], Jussila et al. (Finland) [72], Hovde et al. (Norway) [73], and Pederson et al. (meta-analysis of European studies) [74]. IBD, inflammatory bowel disease; BCC, basal cell carcinoma; NA, not applicable; CD, Crohn's disease; UC, ulcerative colitis.

adenocarcinoma, colorectal carcinoma, and anal carcinoma), biliary tract cancer, and hematological malignancies (myeloma and non-Hodgkin lymphoma). However, a thorough review conducted by European experts recently considered the overall risk of IBD-related cancer to be of limited magnitude [21]. Indeed, a pan-European study revealed – while acknowledging excess risk for certain cancer types – no increased rates of overall cancer in IBD patients [22]. Consistently, a meticulous analysis of the Swiss IBD cohort demonstrated cancer rates that were comparable to the general population based on a follow-up of 12,420.8 patient years [23]. Taken together, the risk of IBD-related cancer overall and specific subtypes appears to be increased, although to a lesser extent than reported in the past. For standardized incidence ratios (SIR) for development of cancer overall, colon cancer, lymphoma, and melanoma (and their respective confidence intervals) reported in the major available cohort studies, see Figure 2. An SIR of 1.0 indicates a rate that is identical to that expected from the general population.

Risk Factors for Cancer Development

Numerous risk factors for the development of intestinal and extraintestinal cancer (including medications) have been identified, although specific pharmaceutical compounds may exhibit both harmful and chemopreventive properties. Two of the best established specific risk factors are (1) extent of colonic disease and (2) disease duration [7]. The more the colonic area is affected and the longer the IBD has been active, the higher the risk for colorectal cancer. These findings have laid the ground for recommendations in terms of screening intervals in IBD patients (see the section Colorectal Cancer). In contrast, patients with isolated rectal disease do not appear to have an increased risk for colorectal cancer [24]. Another well-studied risk factor is the presence of primary sclerosing cholangitis (PSC) [7]. PSC has been shown to increase the risk for both colorectal cancer and cholangiocarcinoma [7, 20, 25, 26]. Patients with PSC should therefore undergo annual screening colonoscopies regardless of IBD activity. In addition, abdominal ultrasonography and/or MRI should be performed every year. Thiopurines have long been known to have a carcinogenic effect. Several cancer types have been associated with the use of azathioprine and 6-mercaptopurine. Among those are lymphoma, urinary tract cancer, and nonmelanoma skin cancer [7, 11–14, 27, 28]. Of note, azathioprine has been associated with excess risk for the development of cancer overall [23]. Best evidence evolves from the French CESAME study. The use of thiopurines was associated with an increased risk of lymphoproliferative disorders; in CD, lymphoma rates were increased, while in both UC and CD, risk for leukemia was higher than what would have been expected from the general population [11]. Of note, the carcinogenic effect of thiopurines appears to be reversible upon the drug's withdrawal. Despite immunosuppressive drugs' potentially deleterious effects, they can also lower cancer risk through controlling inflammation. So, one might assume a vulnerable equilibrium, where either too much inflammation or too much immunosuppression can be harmful. Controlling inflammation could be more important as in 1 study anti-TNF use was associated with an overall decreased risk of cancer development [23]. The involvement of TNF and its role in carcinogenesis is however very complex. While the aforementioned factors are rather specific to IBD, several non-IBD-related factors have been linked to cancer development such as increased age, smoking, and positive family history for cancer.

Protective Factors

Few protective factors have been identified. As previously mentioned, anti-TNF use has been associated with a lower incidence of cancer overall, which might be attributed to a better control of intestinal inflammation [23]. Nonetheless, this finding has to be interpreted cautiously as it is based on a retrospective analysis and could be biased by the fact that patients with high cancer risk are less likely treated with anti-TNF. Data on 5-ASA chemopreventive properties have been conflicting. Few studies have shown decreased rates of colorectal cancer in both UC and CD [17–19], while no such effect was seen in a nonreferral IBD population [29].

Inflammation-Related Malignancies

Ongoing intestinal inflammation has been associated with the following cancer types: colorectal carcinoma, small bowel adenocarcinoma, intestinal lymphoma, anal carcinoma, and cholangiocarcinoma (Fig. 1) [7]. These cancers are potentially preventable with the use of immunosuppressive and biologic agents.

Colorectal Cancer

Colorectal cancer represents the third most common cancer type worldwide [30]. Incidence rates are estimated at 45.8/100,000 for males and 29.2/100,000 for females (National Institute for Cancer Epidemiology and Registration in Switzerland NICER). Survival rates have been

reported to range from 14 to 90% depending on disease stage with an overall 5-year survival rate of 64% (SEER database of the National Cancer Institute, SEER = Surveillance, Epidemiology, and End Results). Because colorectal cancer is so frequent, it might occur in IBD patients just by chance. However, besides these sporadic cases, an association of colorectal cancer with inflammation (so-called colitis-associated cancer) has been clearly established. IBD patients are at increased risk for colorectal cancer except subjects without colonic inflammation. Particular risk factors are extensive colonic disease, long disease duration, severity of colonic disease, and presence of PSC [7]. While patients with ulcerative proctitis are not at increased risk [24], UC patients with left-sided colitis have an intermediate and those with pancolitis have a maximal risk for the development of colorectal cancer [31]. For CD, a colonic involvement of at least 30–50% is considered to result in an excess risk [7, 32]. Frequency of early cancer is low and patients do not seem to be at increased risk during the first 7 years [31]. However, after 6–8 years, the risk for colorectal cancer is higher than that seen in the general population and increases annually in a linear fashion [7, 33]. Based on these findings, the European Crohn's and Colitis Organization (ECCO) developed the following guidelines [31]: after 6–8 years, colonoscopy should be performed (i) annually in case of PSC, colorectal cancer in a first-degree relative younger than 50 years, strictures within the past 5 years, or dysplasia within past 5 years in a patient declining surgery; (ii) every 3 years in case of postinflammatory polyps, colorectal cancer in a first-degree relative older than 50 years, and extensive colitis with moderate to severe activity; and (iii) every 5 years if colitis affects <50% of the colon or if there is extensive colitis with mild activity. Besides IBD-specific risk factors, the following traditional risk factors for colorectal cancer have to be taken into account: male sex, family history, age, smoking, low physical activity, and consumption of red meat and alcohol [7]. Despite the well-accepted concept of colitis-induced carcinogenesis, the increased risk of colorectal cancer in IBD has been questioned lately. No excess risk was found in a Danish study and a recent meta-analysis [20, 33]. There are several explanations for these findings: (1) the introduction of novel and potent immunosuppressive drugs has led to better control of intestinal inflammation; (2) screening strategies have improved; (3) colectomy has been implemented in more countries for high-grade dysplasia; and (4) certain drugs may have chemopreventive properties [23]. However, despite these promising data, it can still be assumed – although to a lesser extent than previously thought – that IBD results in a 2-fold increase in the risk of colorectal cancer [34].

Pathogenesis of IBD-related colon cancer appears to be similar to that of sporadic cases. Inflammation and consecutive inflammatory insults result in the initiation and progression of carcinogenesis [8]. In a first step, changes occur on a molecular level such as TP53 mutations, microsatellite instability, or CpG island methylation [35, 36]. This then leads to histological dysplasia ranging from indefinite to low and finally high-grade dysplastic lesions [37, 38]. Loss of APC, a known tumor suppressor gene mutated in patients with familial adenomatous polyposis (FAP), usually occurs at a late stage [7]. Changes in the microbiota have recently been recognized as a potential contributor to tumor formation. Despite similar pathogenesis, IBD-associated dysplastic lesions are flatter and have less distinct borders compared with sporadic precancerous lesions and are therefore less amenable to early detection and preventive removal during screening colonoscopies [7]. This should be kept in mind when dealing with IBD patients. Dysplastic lesions might be missed with standard endoscopy techniques. Therefore, ECCO recommends either high-definition/chromoendoscopy with targeted biopsies or standard endoscopy with random biopsies (at least 33) [31]. Colectomy should follow if high-grade dysplasia or carcinoma is detected, which is not amenable to endoscopic resection.

Based on the current knowledge, the following approaches are recommended to prevent development of colorectal cancer: (1) colonic disease and inflammation should be controlled as much as possible and (2) screening for colorectal cancer should start 6–8 years after IBD diagnosis or earlier in case of additional risk factors. It remains to be proven whether or not 5-ASA and thiopurines indeed have chemopreventive properties. The benefit from aspirin in IBD patients is unknown and – as of yet – cannot be recommended. Still, IBD patients already taking aspirin for other reasons should keep doing so.

Small Bowel Adenocarcinoma

Adenocarcinoma of the small bowel is a rare disease with a cumulative incidence rate of 30 per 100,000 patient years [39]. However, these rates are considerably higher in IBD patients. Small bowel CD, particularly if long standing, results in an excess risk for small bowel cancer, that is, 20–30 times higher than that seen in the general population [40]. Rates appear to be lower in the anti-TNF

era [23]. In contrast to the colon, the small bowel is not easily amenable to preventive strategies, and optimal screening strategies have yet to be defined. Broad implementation of capsule endoscopy is limited by the risk of capsule retention in case of stenotic disease.

Intestinal Lymphoma

Lymphomas in the intestine are generally rare, but might occur with a frequency of up to 10–48.3 per 100,000 patient years in IBD [23, 41]. Indeed, there appears to be a 3-fold increase in IBD patients compared with the general population [23]. IBD-related lymphomas are typically of the B-cell non-Hodgkin subtype and are found in chronically inflamed intestinal lesions [7, 41]. Particular risk factors for development of intestinal lymphoma are (1) extensive inflammation, (2) middle-aged males, and (3) long disease duration (>8 years) [41]. Since EBV is often detected in intestinal lymphoma cells and association between EBV and lymphoma has been shown for other lymphoma subtypes, inflammation-promoted EBV replication is thought to be a main contributor to this type of malignancy [42].

Anal Carcinoma

Gastroenterologists may be reluctant to screen for anal cancers. A proper rectal examination is essential for the identification of this tumor. Although incidence is low (0.01–0.02/1,000), several risk factors have been identified: males who have sex with males, females with high-grade cervical dysplasia, and presence of fistula in patients with long-standing perianal CD [7, 43]. In the latter, the incidence increases to 0.38 per 1,000 patient years [44]. While anal cancers are usually of squamous epithelial origin and related to HPV infection, cancers arising from fistula can be either adenocarcinoma or squamous cell carcinoma [7]. These cancers are not associated with HPV infection. Prognosis of anal carcinoma is generally poor.

Cholangiocarcinoma

Rates for cholangiocarcinoma appear to be 2–6-fold higher in IBD patients compared with the general population [7, 25, 26]. Reported crude incidence might be as high as 24.2/100,000 [23]. Cholangiocarcinoma is almost uniformly detected in IBD patients with PSC [26]. Here, the risk for cholangiocarcinoma is increased by 160-fold [45]. PSC patients have a life-time risk for cholangiocarcinoma of 5–10% [45]. PSC patients should therefore undergo screening for cholangiocarcinoma, most probably with either annual abdominal MRCP or sonography combined with measuring CA 19–9 serum levels. Most importantly, every PSC patient requires colonoscopy to check for underlying IBD. Coexistence of PSC and IBD is a particular risk factor for the development of colorectal cancer and should urge doctors to perform screening colonoscopies on annual basis [20, 31].

Immunosuppression-Related Malignancies

Both conventional immunosuppressive agents and biologics have been linked to various cancer subtypes, particularly hematological malignancies and skin cancer (both melanoma and nonmelanoma skin cancers; Fig. 1). Several pathomechanisms have been suggested. Immunosuppressive agents may cause tumor formation by altering DNA, impairing immune control of chronic infection by mutagenic viruses such as EBV or HPV, and reducing immunosurveillance of cancer or dysplastic cells [7, 46–48].

Hematological Malignancies

Although IBD does not appear to increase the rates of lymphoma per se (except for the subtype of intestinal lymphoma) [11, 49], NHL have been a particular concern in IBD patients. The use of thiopurines is associated with the development of EBV-associated B-cell lymphoma [11]. Young men seem to be at particular risk (incidence of 3 per 1,000 patient years) [11]. Thiopurines have been associated with a 5- to 6-fold increased risk for lymphoma development [11, 50]. In rare cases, a non-EBV-related hepatosplenic T-cell lymphoma has been described within 2 years after treatment initiation in young men [51]. Therefore, azathioprine and 6-mercaptopurine should be used with caution in this subpopulation and alternative agents should be considered such as methotrexate if combination therapy is needed. Thiopurines have further been associated with the development of acute myeloid leukemia and severe myelodysplastic syndrome [52]. For anti-TNF, data are conflicting. Based on the current literature, it is currently not clear if lymphoma risk is indeed elevated in anti-TNF-treated IBD patients [15, 23], but long-term dose accumulation could potentially increase this risk. Increased rates of lymphoma have been reported in rheumatologic studies.

Skin Cancer

Skin cancer is a frequent problem even in young patients; therefore, occurrence of dermatologic malignan-

cies in the IBD population is not surprising. Both thiopurines and anti-TNF have been linked to the development of skin cancers. Azathioprine and 6-mercaptopurine have been associated with an increased risk of nonmelanoma skin cancer [13, 14], while no such risk has been seen for anti-TNF. However, the latter has been associated with development of melanoma [15, 16]. Studies reported a 1.5–4-fold increased risk [15, 16, 23]. There appears to be an intrinsic risk for melanoma in IBD that cannot be explained by the use of immunosuppressive agents. Based on these findings, IBD patients should be regularly seen by a dermatologist for evaluation of possible early skin cancer lesions [34]. This is particularly recommended for patients with light skin types and for those on thiopurines and/or anti-TNF treatment.

Cervical Cancer

In few studies, increased rates of cervical cancer have been reported in women with IBD. Cervical cancer is typically associated with HPV infection. As of yet, it remains unclear if this is due to an intrinsic risk or due to immunosuppression [53]. In general, the rates of cervical cancer have been decreasing over the last decades due to wide implementation of screening strategies. In addition, HPV vaccination has been widely introduced into clinical practice. In Switzerland, this vaccination is strongly recommended for all women aged 11–14. Women up to the age of 26 are encouraged to get vaccinated. Costs are fully covered as part of the cantonal vaccination programs. Women with IBD falling into this age category should be particularly encouraged to undergo vaccination given the clear and well-accepted association between HPV infection and development of cervical cancer. They should further see their gynecologist every 1–2 years. HPV-related infections are less frequently observed in men than women. Still, HPV vaccination should be recommended for male subjects.

Urinary Tract Cancer

Use of thiopurines has been associated with increased rates of kidney and bladder cancer in transplant recipients [54]. Similar findings have been shown in the IBD population, although the risk is almost completely restricted to older males, particularly smokers [27, 55]. No such increase was seen with the use of anti-TNF [15]. In patients with a previous history of urogenital cancer and the need for immunosuppressive therapy, use of thiopurines should be avoided. The role of screening strategies in patients on thiopurine treatment (such as urine cytology and/or cystoscopy) remains to be determined.

Future Perspectives

The introduction of anti-TNF into clinical practice has dramatically changed IBD management. Newer non-anti-TNF biologics further will. Clinicians dealing with IBD now have a wide armamentarium of options for the treatment of CD and UC: anti-integrins, anti-IL-12/23, and the newest kid on the block, JAK-inhibitors. Data on their safety profile with regard to cancer development are currently emerging. Analysis of the GEMINI long-term safety data and postmarketing setting did not show any association of the anti-integrin vedolizumab with increased malignancy incidence (5,670 patient years) [56]. The JAK-inhibitor tofacitinib has not been associated with increased risk for nonmelanoma skin cancer and other malignancies based on a meta-analysis including 82 studies (66,159 patients) [57]. Lastly, the anti-IL-12/23 antibody ustekinumab does not appear to increase the risk of cancer development (nonmelanoma skin cancers and other malignancies) [58, 59]. Analyses of clinical extensions in psoriasis and psoriatic arthritis with a follow-up of 5 and 2 years, respectively, are reassuring. However, given a considerably higher number of cancer cases in UC patients treated with ustekinumab compared with placebo, the association between anti-IL-12/23 and malignancy in IBD warrants further investigation [60]. In particular, longer follow-up studies are needed (for all non-anti-TNF biologics) in order to assess possible dose accumulation effect over time.

Tumor screening strategies are important and effective tools for the prevention and early detection of cancer in the general population and IBD patients. However, data for their efficacy evolve from case series and retrospective case-control studies (demonstrating reduced rates of colorectal cancer and improved survival) [61–67]. Randomized-controlled trials showing a clear benefit from colonoscopy in IBD are still lacking [31]. Chromoendoscopy with targeted biopsies has been demonstrated to increase dysplasia detection rate [68]. The role of newer tools such as narrow-band imaging and endomicroscopy remains unclear. Trials are required to define their place in the screening algorithm. Further studies are needed with regard to screening strategies for cholangiocarcinoma, small bowel adenocarcinoma, and urinary tract cancer. From a personalized medicine perspective, it will be interesting to see which IBD phenotypes are at particular risk for specific cancer subtypes. This will help to individually tailor screening recommendations as well as therapeutic strat-

egies in the future. As of yet, the following recommendations can be made: thiopurines should be avoided in patients with a prior history of lymphoma, acute myeloid leukemia, myelodysplastic syndrome, nonmelanoma skin cancer, and urinary tract cancer, while anti-TNF should not be used in patients with a history of melanoma [34, 69]. In addition, ECCO guidelines recommend to limit the use of thiopurines in EBV seronegative young men.

Conclusions

Although recent studies and meta-analyses questioned the excess rates of cancer in IBD patients, IBD still is associated with cancer development due to ongoing intestinal inflammation and the use of potential carcinogenic drugs. The latter has been particularly shown for thiopurines and anti-TNF. However, more recent data from the Swiss IBD cohort revealed that the overall risk for cancer might be even lowered with the use of anti-TNF indicating that there could be a net benefit from these agents [23]. This might be attributed to their potential of deeply controlling intestinal disease activity. Patients should be educated about the increased risk of cancer with IBD and IBD drugs. However, they should also be informed that most malignancy subtypes are possibly preventable by controlling intestinal inflammation and by using adequate screening strategies. Data on the use of chemopreventive agents (5-ASA, azathioprine, and aspirin) for the pure purpose of cancer prevention is too conflicting to give any recommendations. However, these drugs should be used for IBD treatment (5-ASA and azathioprine) or continued if used for other indications (aspirin).

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Author Contributions

T.G., S.R.V., and M.S.: study conception and design and drafting of the manuscript. A.K. and L.B.: critical revision of the manuscript for intellectual content.

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